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HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING,
AND METHODS FOR EVALUATING RISK OF NEURAL TUBE
DEFECTS, CARDIOVASCULAR DISEASE, AND CANCER

Roy A. Gravel et al.

Filing Date: August 10, 1999

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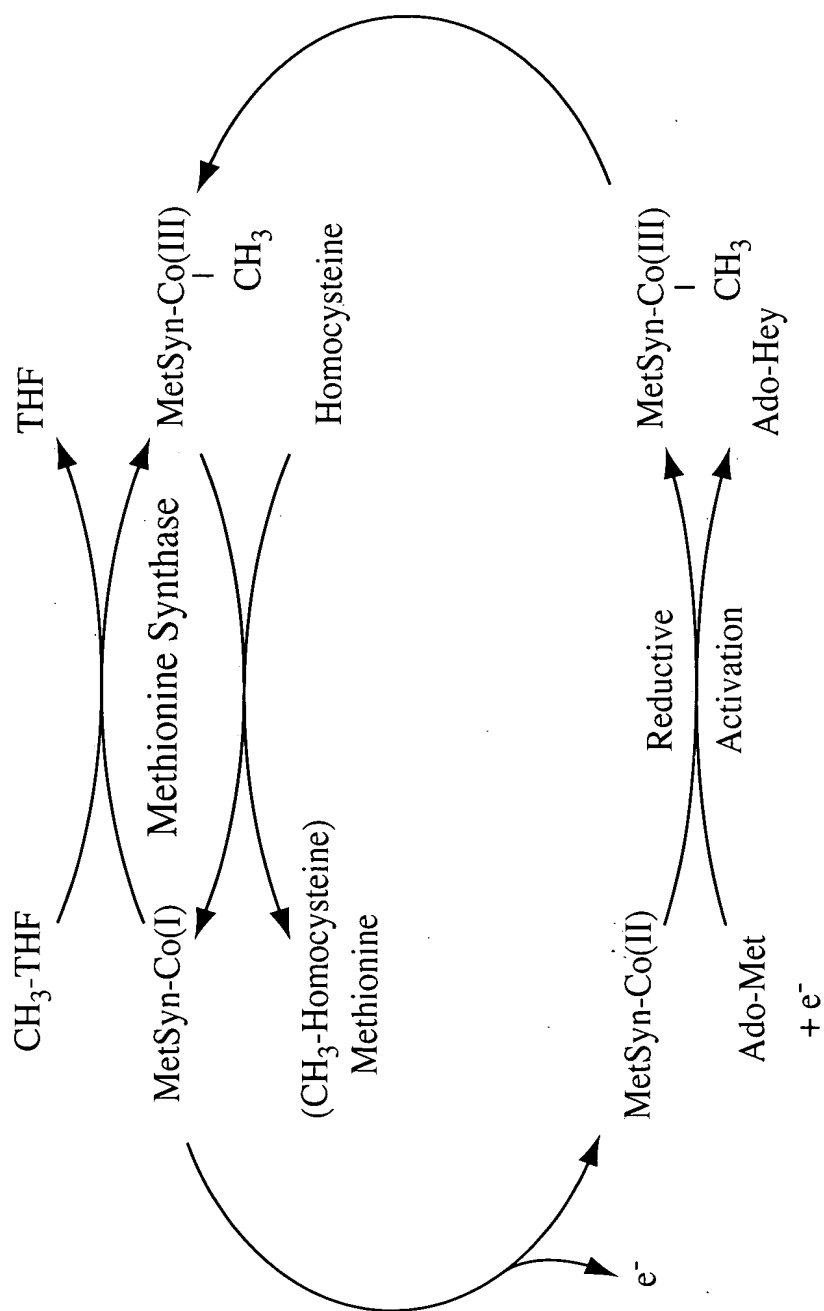
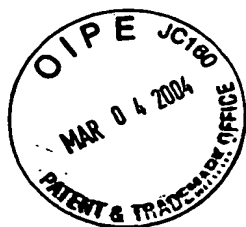


Fig. 1



HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING,
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CAAGTTGGTGAAGTCGCGTGTGTCAGGTTGTCGCCGGCTGGCGGGCGGTGTTTCACTGTACATGCCCTTCAAGTG
1 ATGAGGAGGTTTCTGTACTATATGCTACACAGGAGGAGGCAATGTCGAGCAAGCTGTGGTACATGGATTTTCGAGATCTTCACTGTATTAGTGAA
M R R F L L L Y A T Q Q G Q A K A I A E M C E Q A V V H G F S A D L H C I S E 40
121 TCCGTAAGTATGACCTAAACCGAAACAGCTCTCTTGTGTGTTTCTACACGGGACCGGAGACCCACCCGCAAGTTTGTAAAGAAATACAGAACCAACA
S D K Y D L K T E T A P L V V V S T T G T G D P P D T A R K F V K E I Q N Q T 80
241 CTGCCGGTGAATTCCTTGTCTACCTCGGTTACTGGTTACGAAATACACCTACTTTTGCATGGGGGAAGATAATGATAAACGACTTCAAGAGCTTGGAGCC
L P V D F A H L R Y G L G L G D S E Y T Y F C N G G K I I D K R L Q E L G A 120
361 CGGCATTCTATGACACTGGACATGCAGATGCTGTAGTTAGAACCTGTGGTGGCGTGGATCTGGCACTCTGGCCACCCCTCAGAAAGCATTTTAGGTCAAGCAGAGGACAA
R H F Y D T G H A D D C V G L E L V V E P W I A G L W P A L R K H F R S S R G Q 160
481 GAGGAGATAAGTGGCGCACTCCCGGTGGCATCACTGCAATCCTTGAGGACAGACCTTGTAAGTCAGAGCTGCTACACATTGAATCTCAAGTCGAGCTTCTGAGATTGCGATTCAGGA
E E I S G A L P V A S P A S L R T D L V K S E L L H I E S Q V E L L R F D D S G 200
601 AGAAGGATTCTGAGGTTTGAAGCAAAATGCACTGAACAGCAACCAATCCAATGTTGAATGAAGACTTTGAGTCTCTCACTTACCCGTTCCGTTACCCCACTCTCACAAGCCTCTCTG
R K D S E V L K Q N A V N S N Q S N V I E D F E S S L T R S V P P L S Q A S L 240
721 AATATTCCTGTTTACCCCAAGATATTACAGGTACATCTGCGAGGAGTCTCTGGCCAGGAGAAAGCCAAAGTATCTGTGACTTCAGCAGATCCAGTTTTCAGTGCCCAATTTCAAAG
N I P G L P P E Y L Q V H L Q E S L G Q E E S Q V S V T S A D P V F Q V P I S K 280
841 GCAGTTCACTTACGAATGATGCCATAAAACCACTCTGCTGTAGATTTGACATTTCAANTACAGACTTTTCTATCAGCTGGAGATGCCCTTCAGCGTGATCTGCCCTAACAGT
A V Q L T T N D A I K T T L L V E L D I S N T D F S Y Q P G D A F S V I C P N S 320
961 GATTCGTGAGTACAAAGCCTACTCCAAAGACTGCAGCTTGAAGATAAAGAGAGCACTGCGTCTTTTGAATAAAGGAGAGGAGTACCTTACCCCAAGCATATA
D S E V Q S L L Q R L Q L E D K R E H C V L L K I K A D T K K G A T L P Q H I 360
1081 CCTGCGGGATGTTCTCTCCAGTTTCTTACCTGGTGTCTTGAATCCGAGCAATTCCTAAAGGCAATTTTTCGAGCCCTTGTGGACTATACAGTGACAGTGTGTAAGCGCAGG
P A G C S L Q F I F T W C L E I R A I P K K A F L R A L V D Y T S D S A E K R R 400
1201 CTACAGGAGCTGTGCAGTAAACAGGGCAGCCGATTATAGCCGTTTGTACGAGATGCCCTGCTGTGGATCTCCTCGCTTCCCTTCTTGGCCAGCCACCTCAGTCTC
L Q E L C S K Q G A A D Y S R F V R D A C A C L L L D L L L A F P S C Q P P L S L 440

Fig. 3-1



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CAAGTTGGTGAAGTCGGTTGTGCAAGTTCTGTCGCCGGCTGGCGCGGCTGTTTCACTGTACATGCCCTGAAGTG
1 ATGAGGAGGTTTCTGTTACTATATGCTACAGCAGGAGCAGGCAAGGCCATCGCAGAAGAAATGTGTGAGCAAGCTGTGGTACATGGATTTCTGCAGATCTTCACTGTATTAGTGAA
M R R F L L L Y A T Q Q Q A K A I A E E M C E Q A V V H G F S A D L H C I S E 40
TCCGATAAGTATGACCTAAACCGAAACAGCTCCTCTTGTGTTGTTTCTACACGGGACCGGAGACCCACCGACACAGCCCGCAAGTTGTTAAGAAATACAGAACCAACA
S D K Y D L K T E T A P L V V V S T T G T G D P P D T A R K F V K E I Q N Q T 80
241 CTGCCGGTTGATTTCTTGTCTACCTGGGTATGGTTACTGGTCTCGGTGATTGAGAATACACCTACCTTTTGCATATGGGGGGAAGATTAATTGATAAACGACTTCAAGAGCTTGGAGCC
L P V D F F A H L R Y G L L G L G D S E Y T Y F C N G G K I I D K R L Q E L G A 120
361 CGGCATTCTATGACACTGGACATGCATGCTGTGTAGGTTTAGAATCTGTGTGAGCCGTTGAGCTGCTGCACTCTGGCCAGCCCTCAGAAAGCATTTTAGTCAAGCAGAGGACAA
R H F Y D T G H A D D C V G L E L V V E P W I A G L W P A L R K H F R S S R G Q 160
481 GAGGAGATAAGTGGCGCACTCCGGTGGCATCACCTGCATCCTTGAGGACAGACCTTGTGAAGTCAGAGCTGCTACATTAATCTCAAGTCGAGTTCGATTCGATTCAGGA
E E I S G A L P V A S P A S L R T D L V K S E L L H I E S Q V E L L R F D D S G 200
601 AGAAGGATTTGAGGTTTGAAGCAAAATGCACTGAACAGCAACCAATCCAAATGTTGAATGAAGACTTTGAGTCTCTCACTTACCCGTTGGTACCCCACTCTCAAGCCTCTCTG
R K D S E V L K Q N A V N S N Q S N V V I E D F E S S L T R S V P P L S Q A S L 240
721 AATATCCTGGTTTACCCCAAGATTTTACAGGTACATCTGCAAGGAGTCTCTGGCCAGGAGAAAGCAAGTATCTGTGACTTCAGCAGATCCAGTCTTCAAGTGCCCAATTCAAAG
N I P G L P P E Y L Q V H L Q E S L G Q E E S Q V S V T S A D P V F Q V P I S K 280
841 GCAGTCAACTTACTAGGAATGCCATAAAACCACTCTGCTGGTAGAATGGACATTTCAAAATACAGACTTTTCCCTATCAGCCTGGAGATGCCCTTCAGCGTGATCTGCCCTAACAGT
A V Q L T T N D A I K T T L L V E L D I S N T D F S Y Q P G D A F S V I C P N S 320
961 GATTCTGAGGTACAAAGCCTACTCCAAAGACTGACGCTTGAAGATAAAGAGAGCACTGCGTCTCTTTTGAATAAAGGAGAGACACAAAGAGAGAGGAGTACCTTACCCCAAGCATATA
D S E V Q S L L Q R L Q L E D K R E H C V L L K I K A D T K K K G A T L P Q H I 360
1081 CCTGGGGAGTGTCTCTCCAGTTCATTTTACCTGGTGTCTTGAATCCAGCAATTCCTAAAGGCAATTTTTCGAGCCCTTGTGGACTATACAGTGACAGTGTGTGAAGCCGAGG
P A G C S L Q F I F T W C L E I R A I P K K A F L R A L V D Y T S D S A E K R R 400
1201 CTACAGGAGTGTGCAGTAAACAGGGCAGCGATTATAGCCGTTTGTACGAGATGCCCTGTGCTGCTGTTGGATCTCCTCTCGCTTCCCTTCTTGGCAGCCACCACTCAGTCTC
L Q E L C S K Q G A A D Y S R F V R D A C A C L L D L L A F P S C Q P P L S L 440

Fig. 3-3

1321 CTGCTCGAACATCTTCCTAAACTTCAACCCAGACCATATTCTGTGCAAGCTCAAGTTATTTCACCCAGGAAGCTCCATTTTCTCTTCAACATTTGTGGAATTTCTGTCTACTGCCACA
L L E H L P K L Q P R P Y S C A S S L F H P G K L H F V F N I V E F L S T A T 480

1441 ACAGAGTTCTGCGAAGGAGTATGTACAGGCTGGCTGGCTTGTGTTGCTTCAGTTCTTCAGGCCAAACATACATGCATCCCATGAAGACACGCGGGAAGCCCTGGCTCTCTAAGATA
T E V L R K G V C T G W L A L L V A S V L Q P N I H A S H E D S G K A L A P K I 520

1561 TCCATCTCTCTCGAACACAAATTTTCCACTTACAGATGACCCCTCAATCCCATCATATAATGGTGGTCCAGGAACCGGATAGCCCCGTTTATTGGGTTCTCTACAAACATAGAGAG
S I S P R T T N S F H L P D D P S I P I I M V G P G T G I A P F I G F L Q H R E 560

1681 AAATCCAGAACAACACCCAGATGGAAATTTTGGAGCAATGTGTGTTGTTTTGGCTGCAGCATAGGATAGGATTATCTATTAGAAAAGAGCTCAGACATTTCTCTTAAGCATGGG
K L Q E Q H P D G N F G A M W L F F G C R H K D R D Y L F R K E L R H F L K H G 600

1801 ATCTTAATCATTAAGGTTTCTTCTCAAGAGATGCTCCTGTGGGAGGAGGAACCCAGCAAAAGTATGTACAAGACAACATCCAGCTTCATGGCCAGCAGGTGGCGGAGAATCTCTC
I L T H L K V S F S R D A P V G E E E A P A K Y V Q D N I Q L H G Q Q V A R I L 640

1921 CTCAGGAGAACGGCCATATTATGTGTGGAGATGCAAGAATATGGCAAGGATGATGCCTTGTGCAATAATAAGCAAGAGGTTGGAGTTGAAAACACTAGAAGCAATG
L Q E N G H I Y V C G D A K N M A K D V H D A L V Q I I S K E V G V E K L E A M 680

2041 AAAACCTGGCCACTTTAAAGAGAAAACGCTACCTTCAGGATATTGTGTCATAAAACCAGAAATTAAGAAAGGATTAAGCTTTTTTGACTGAAAGTACTAAAAGTCAGCTTTAC
K T L A T L K E E K R Y L Q D I W S ***

2261 TAGTGC AAAACCTTTAAATTTTCAAAGAAAATTTTCTTCAAACATTTCTTGAAGGACATGGAGTGGATTCATTTAACATAATAACAAAACCTTCTCTGATTGATTTTACGTATC
TTCTATCTACGCCCTTCTGTGCTGTGACTCTCCCAAAATGCCCTGTGCTGTGACTCTCTGAGCTAAGGCAGCTTCAGTCCCTATCAGCGCCCTCTTACTTCCAGAGAACT
TCAGAGACTCTGTCTCCATGCAAGGTTCTTGAAATAGGGAGACTGACTGAGTAGTCTCATTTCTGTGACTTACAGTGGCAACATTTAAAAAAGTATGAAAATGATTTATTTTCTG
22521 TATGATGATATACCATAAAGAAATGTCATATTAATGTAATTAACATGTAGACATATCTGTTATATGTTATGTAACATCAATGGTTATTTGTGTACTAAAGCTATATTCTGTG
22641 ATAAAAATATTTTAGGATAATTGGCTACAGAGGATTTATTTTATGATGCTGGGAAATATGAAATGTATTTTAAAAATTCACCTCTGGCATATGGATTATCTATCACCATTACTTTT
22761 TTTTAAAGTCACAAATTTTCAGAAATTTTGGGACATTTGCAATTCATTTACAGGTACCAGTACGATACATATTTTAAAGAAAGATACAACTTTTATTTTCACTCTCTTTATTTCTGCTGCTT
22881 GGCACATTTTGTAGTTTTCACATATTTGTCTCCATGATACCACCTCAAGCAGTGTGCTGACCTAAAAATACGTACTTAGTATCCTTGGATTTTGTAGATTTCCCACTGTCTTAAT
33001 TCCTGTGTATAATTTGCACAAACAAAATGTTATGATAATCTTTCTCCACTGTTCTAATATATATTTGTTATTTTATTTGTAGCTGGGATTTTAAACATCTCTGTGTGAAGGCTTT
3121 TGATCTTTTGGAGAAATAAGATCTGGAAGAAATGGCATAATCTTAAAAAATAAAAAAATAAAAAA

Fig. 3-4



HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING,
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HsMTRR	-----	
CeMTRR	-----	
HsCPR	MGDSHVDTSSTVSEAVAEVSLFSMTDMILFSLIVGLLTYWFLFRKKKEE	50
	FMN	
HsMTRR	-----MRRFLLLYATQQGQAKAIAEEMCE	24
CeMTRR	-----MTDFLIAFGSQTGQAETIAKSLKE	24
HsCPR	VPEFTKIQTLTSSVRESSFVEKMKKTGRNIIVFYGSQTGTAEFANRLSK	100
 * * * * . .	
	FMN	
HsMTRR	QAVVHGFSADLHCISESDK-YDLKT-----ETAPLVVVVSTTGTGDP	66
CeMTRR	KAELIGLTPRLHALDENEEKFNLE-----EKLC-AIVVSSTGDGDAP	66
HsCPR	DAHRYG---MRGMSADPEEYDLADLSSLPEIDNALVVFCMATYGECDPT	146
	* * * * * *	
	FMN	
HsMTRR	DTARKFVKEIQNQTLPVDFFAHLRYGLLGLGDSFYTYFCNGGKIIDKRLQ	116
CeMTRR	DNCARFVRRINRNSLENEYLKNLDYVLLGLGDSNYSSYQTIPRKIDKQLT	116
HsCPR	DNAQDFYDWLQETDVD---LSGVKFAVFLGNGKTYEHFNAMKYVDKRLE	193
	* * * * * * * * *	
HsMTRR	ELGARHFYDTGHADDCVGLLELVPEWPIAGLWPALRKHFRRSSRGQEEISGA	166
CeMTRR	ALGANRLFDRAEADDQVGLLEVEPEWIEKFFATLASRFDISADKMN----	162
HsCPR	QLGAQRIFELGLGDDDGNEEDFITWREQFWPAVCEHF-----GV	233
	*** . . . * * * * . . . *	
HsMTRR	LPVASPASLRTDLVKSELLHIESQVELL--RFDDSGRKDSEVLKQNAVNS	214
CeMTRR	-AITESSNLKLNQVKTE----EEKKALLQKRIEDEESDDEGRGRVIGID-	206
HsCPR	EATGEESSIRQYEL-----VVHTDIDAAKVVMGEMGRKLSYEN	271
	
HsMTRR	NQSNVVIDF---ESSLTRSVPLS-QASLNIPGLPPEYLQVHLQESLGQ	260
CeMTRR	---MLIPEHYDYPEISLLKGSQTLSNDENLRVPIAPQPFIVSSVSNRKLP	253
HsCPR	QKP-----PFD-----AKNPFLAAVTNTRKLN	293
	
HsMTRR	EESQVS-----VTSADPVFQVPISKAVQLTT--NDAIKTTLLVELDIS	301
CeMTRR	EDTKLEWQNLCKMPGVVTKPFEVLVVSAAEFVTDPFSSKIKTKRMITVDFG	303
HsCPR	QGTE-----RHLMHLELD	306
	
HsMTRR	N--TDFSYQPGDAFSVICPNSDSEVQSLLQR-LQLEDKREHCVLLKIKAD	348
CeMTRR	DHAAELQYEPGDAIYFCVPNPALEVNFILKRCGVLDIADQQCEL-SINPK	352
HsCPR	ISDSKIRYESGDHVAVYPANDSALVNQLGK---ILGADLD--VVMSSLNNL	351
	. * * * * *	
HsMTRR	TKKKGATLPQHIPAGCSLQFIFTWCLEIRAIKKAFLRALVDYTSDSAEC	398
CeMTRR	TEKINAQIPGHVHKITTLRHMTTCLDIRRAPGRPLIRVLAESTSDPNEK	402
HsCPR	DEESNKKHP--FPCPTSYRTALTYLDITNPPRTNVLYELAQYASEPSEQ	399
	* . . * * * * . . . * . . *	

Fig. 4-1



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HsMTRR	RRLQEL--CSKQGAADYSRFVRDACACLLDLLLAFPPSCQPPLSLLLEHLP	446
CeMTRR	RRLLEL--CSAQGMKDFTFVVRTPGLSLADMLFAFPNVKPPVDRLELLP	450
HsCPR	ELLRKMASSSGEGKELYLSWVVEARRHILAILQDCPSLRPPIDHLCCELLP	449
	* . * . * . * . * * * * *	
	<u>FAD</u> <u>FAD</u> <u>FAD</u>	
HsMTRR	KLQPRPYSCASSSLFHPGKLHFVFNIVEFLSTATTEVLRKGVCTGWLALL	496
CeMTRR	RLIPRPYSMSS---YENRKARLIYSEMEFPATDGRRHRSRKGGLATDWLNSL	497
HsCPR	RLQARYYSIASSSKVHPNSVHICAVVVEYETKAGR--INKGVATNWL---	494
	. * * * * . * . . * * . * *	
HsMTRR	VASVLQPNIHASHEDSGKALAPKISISPRTTNSFHLP-----DDPSIP	539
CeMTRR	R-----IGDKVQVLGKEPARFRLPPLGMTKNSAGKLP	529
HsCPR	RAKE-----PVGENGGRALVPMFVRKSQFRLPFK-----ATTP	527
	* *	
	<u>NADPH</u>	
HsMTRR	IIMVGPGTGIAPIFIGFLQHREKLQEHPDGNFGAMW-LFFGCRHKDRDYL	588
CeMTRR	LLMVGPGTGVSVFLSFLHFLRKLKQDSPSDFVDVPRVLFFGCRDSSVDAI	579
HsCPR	VIMVGPGTGVAPFIGFIQERAWLRQQGKE--VGETLLYYGCRRSDEDYL	574
	..*****. * . * . * .. * . * * *	
	<u>NADPH</u> <u>NADPH</u>	
HsMTRR	FRKELRHFLKHGILTHLKVVSFSRDAPVGEEEAAPAKYVQDNIQLHGQQVAR	638
CeMTRR	YMSELEMFVSEGILTDLIICESEQ-----KGERVQDGLRKYLDKVL	621
HsCPR	YREELAQFHRDGAQTQLNVAFSRE-----QSHKVYVQHLLKQDREHLWK	618
	. * * * * * * * * * * * *	
	<u>NADPH</u>	
HsMTRR	ILLQE-NGHIYVCGDAKNMAKDVHDLVQIISKEVGVEKLEAMKTLATLK	687
CeMTRR	FLTASTESKIFICGDAKGMSKDVWQCFSDIVASDQGIPLDLEAKKKLMDLK	671
HsCPR	LI--EGGAHIYVCGDARNMARDVQNTFYDIVAELGAMEHAQAVDYIKKLM	666
	. * . * * * * . * . * * . * . . * . *	
	<u>NADPH/FAD</u>	
HsMTRR	EEKRYLQDIWS	698
CeMTRR	KSDQYIEDVWG	682
HsCPR	TKGRYSLDVWS	677
	* * *	

Fig. 4-2



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HsMTRR	-----	
CeMTRR	-----	
HsCPR	MGDSHVDTSSTVSEAVAEVSLFSMTDMILFSLIVGLLTYWFLFRKKKEE	50
	FMN	
HsMTRR	-----MRRFLLLYATQQGQAKAIAEEMCE	24
CeMTRR	-----MTDFLIAFGSQTGQAETIAKSLKE	24
HsCPR	VPEFTKIQTLTSSVRESSFVEKMKKTGRNIIVFYGSQTGTAEFANRLSK	100
 * * * * . .	
	FMN	
HsMTRR	QAVVHGFSADLHCISESDK-YDLKT-----ETAPLVVVVSTTGTGDP	66
CeMTRR	KAELIGLTPRLHALDENEEKFNLE-----EKLC-AIVVSSTGDGDAP	66
HsCPR	DAHRYG---MRGMSADPEEYDLADLSSLPEIDNALVVFVCMATYGECDPT	146
	* * * * * *	
	FMN	
HsMTRR	DTARKFVKEIQNTLPVDFFAHLRYGLLGLGDSEYTYFCNGGKIIDKRLQ	116
CeMTRR	DNCARFVRRINRNSLENEYLKNLDYVLLGLGDSNYSSYQTIPRKIDKQLT	116
HsCPR	DNAQDFYDWLQETDVD---LSGVKFAVFLGNGKTYEHFNAMKGYVDKRL	193
	* * * * * * * * *	
HsMTRR	ELGARHFYDTGHADDCVGLLELVVEPWIAGLWPALRKHFSSRGQEEISGA	166
CeMTRR	ALGANRLFDRAEADDQVGLLEVEPWIEKFFATLASRFDISADKMN---	162
HsCPR	QLGAQRIFELGLGDDDNLEEDFITWREQFWPAVCEHF-----GV	233
	*** * * * * *	
HsMTRR	LPVASPASLRDVLKSELLHIESQVELL--RFDDSGRKDSEVLKQNAVNS	214
CeMTRR	-AITESSNLKLNQVKTE----EEKKALLQKRIEEDSDDEGRGRVIGID-	206
HsCPR	EATGEESSIRQYEL-----VVHTDIDAAKVVMGEMGRLKSYEN	271
	
HsMTRR	NQSNVVIEDF---ESSLTRSVPLS-QASLNIPGLPPEYLQVHLQESLGQ	260
CeMTRR	---MLIPEHYDYPEISLLKGSQTLSNDENLRVPIAPQPFIVSSVSNRKLP	253
HsCPR	QKP-----PFD-----AKNPFLAAVTTRNKLN	293
	
HsMTRR	EESQVS-----VTSADPVFQVPISKAVQLTT--NDAIKTTLLVELDIS	301
CeMTRR	EDTKLEWQNLCKMPGVVTKPFEVLVVSAAEFVTDPFSSKIKTKRMITVDFG	303
HsCPR	QGTE-----RHLMHLELD	306
	
HsMTRR	N--TDFSYQPGDAFSVICPNSDSEVQSLLQR-LQLEDKREHCVLLKIKAD	348
CeMTRR	DHAAELQYEPGDAIYFCVPNPALEVNFILKRCGVLDIADQQCEL-SINPK	352
HsCPR	ISDSKIRYESGDHVAVYPANDSALVNQLGK---ILGADLD--VVMSSLNNL	351
	. * * * * *	
HsMTRR	TKKKGATLPQHIPAGCSLQFIFTWCLEIRAIKKAFLRALVDYTSDSA	398
CeMTRR	TEKINAQIPGHVHKITTLRHMTTCLDIRRAPGRPLIRVLAESTSDPNEK	402
HsCPR	DEESNKKHP--FPCPTSRYTALTYILDITNPRTNVLVELAQYASEPSEQ	399
	* . . * * * * *	

Fig. 4-3



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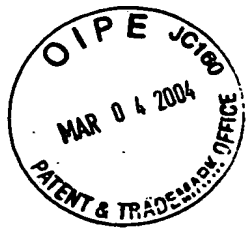
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HsMTRR	RRLQEL--CSKQGAADYSRFVRDACACLLDLLLAFSPCQPPLSLLLEHLP	446
CeMTRR	RRLLEL--CSAQGMKDFDFVTRTPGLSLADMLFAFPNVKPPVDRLELLP	450
HsCPR	ELLRKMASSSGEGKELYLSWVVEARRHILAILQDCPSLRPPIDHLCCELLP	449
	* . * . * . * . * . * . * . * . * . * . *	
	FAD FAD FAD	
HsMTRR	KLQPRPYSCASSSLFHPGKLHFVFNIVEFLSTATTEVLRKGVCTGWLALL	496
CeMTRR	RLIPRPYSMSS---YENRKARLIYSEMEFPATDGRRHRSRKGGLATDWLNSL	497
HsCPR	RLQARYYSIASSSKVHPNSVHICAVVVEYETKAGR--INKGVATNWL---	494
	. * * * * . * . . * . * . * . *	
HsMTRR	VASVLQPNIHASHEDSGKALAPKISISPRTTNSFHLP-----DDPSIP	539
CeMTRR	R-----IGDKVQVLGKEPARFRLPPLGMTKNSAGKLP	529
HsCPR	RAKE-----PVGENGGRALVPMFVRKSQFRLPFK-----ATTP	527
	* *	
	NADPH	
HsMTRR	IIMVGPGGTGIAPFIGFLQHREKLQEHPDGNFGAMW-LFFGCRHKDRDYL	588
CeMTRR	LLMVGPGGTGVSVFLSFLHFLRKLKQDSPDFVDVPRVLFFGCRDSSVDAI	579
HsCPR	VIMVGPGGTGVAPFIGFIQERAWLRQQGKE--VGETLLYYGCRRSDEDYL	574
	..*****. * . * . * . * . * . *	
	NADPH NADPH	
HsMTRR	FRKELRHFLKHGILTHLKVFSRDPVGEAAAPAKYVQDNIQLHGQOVAR	638
CeMTRR	YMSELEMFVSEGILTDLIICESEQ-----KGERVQDGLRKYLDKVLPL	621
HsCPR	YREELAQFHRDGAALTQLNVAFSRE-----QSHKVYVQHLLKQDREHLWK	618
	. ** * * * * . * . * . *	
	NADPH	
HsMTRR	ILLQE-NGHIYVCGDAKNMAKDVDALVQIISKEVGVKELEAMKTLATLK	687
CeMTRR	FLTASTESKIFICGDAKGMSKDVMQCFSDIVASDQGIPLDLEAKKKLMDLK	671
HsCPR	LI--EGGAHIYVCGDARNMARDVQNTFYDIVAELGAMEHAQAVDYIKKLM	666
	. * . * * * . * . * . * . * . *	
	NADPH/FAD	
HsMTRR	EEKRYLQDIWS	698
CeMTRR	KSDQYIEDVWG	682
HsCPR	TKGRYSLDVWS	677
	* * . *	

Fig. 4-4



HUMAN METHIONINE SYNTHASE REDUCTASE: CLONING,
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DEFECTS, CARDIOVASCULAR DISEASE, AND CANCER

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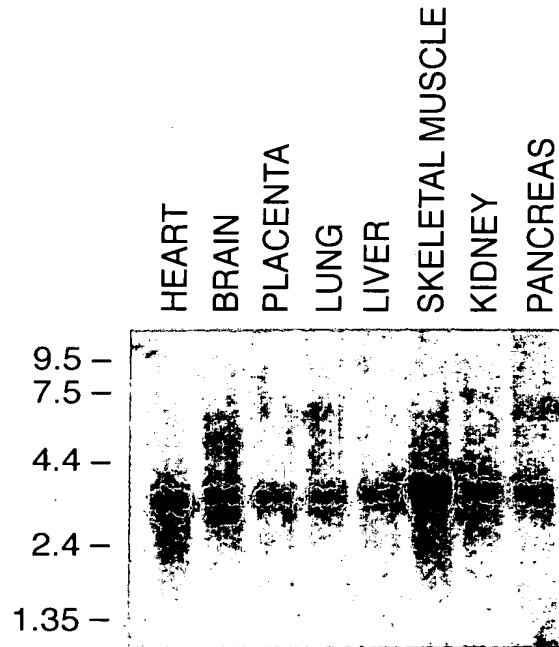
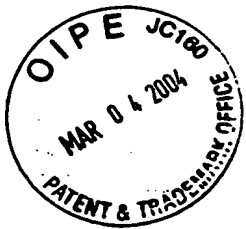


Fig. 5A



Fig. 5B



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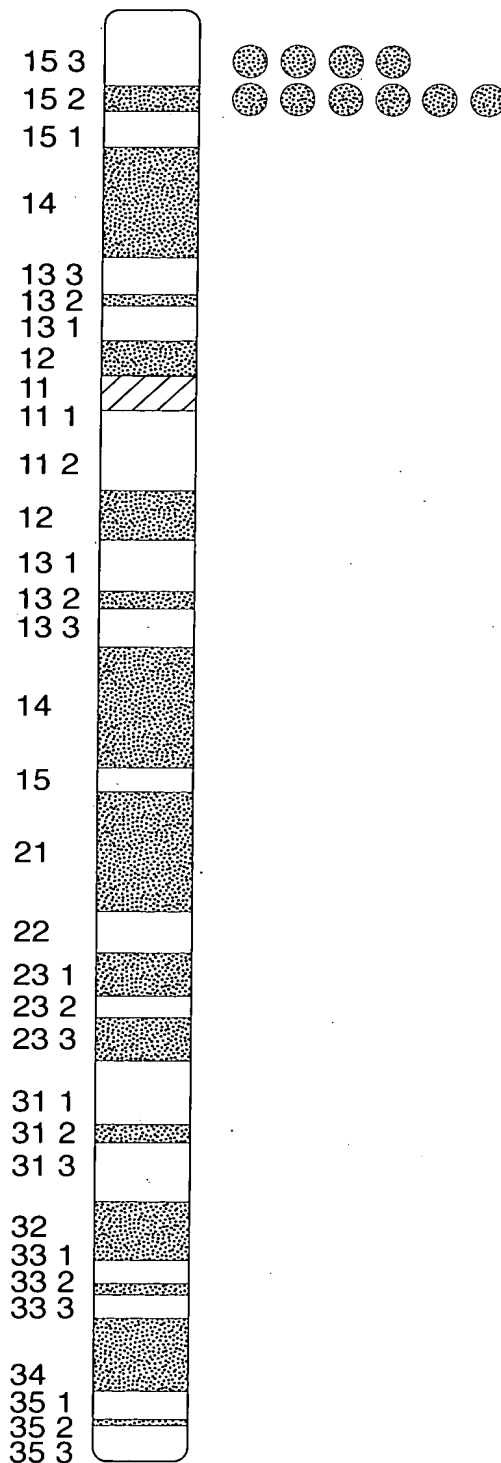
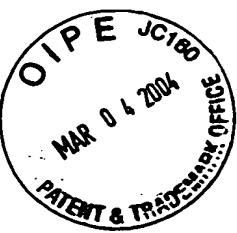


Fig. 6



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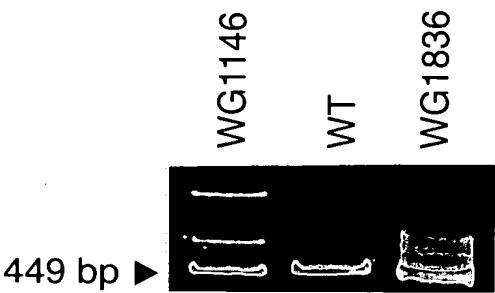


Fig. 7A

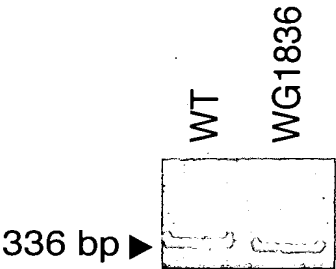
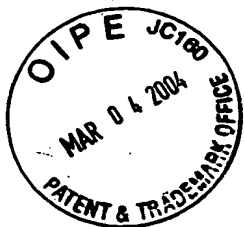


Fig. 7B

Position	Sequence	Accession#	Protein	Organism
572	GAMW [▲] LFFGCRHKDRDYLF	(AF025794)	MTRR	(H sapiens)
558	GETLLYYGCRSDEDYLY	(A60557)	CPR	(H sapiens)
559	GETLLYYGCRRAAEDYLY	(D00101)	CPR	(O cuniculus)
560	GESILYFGCRKRSEDYIY	(X93090)	CPR	(D melanogaster)
572	GPALLFFGCRNRQMDFIY	(P37116)	CPR	(V radiata)
573	GPTVLFFGCRKSDEDFLY	(Z26938)	CPR	(A niger)
1281	CPMVLVFGCRQSKIDHIY	(D16408)	NOS I	(H sapiens)
1009	GRMTLVFGCRRPDEDHIY	(U05810)	NOS II	(H sapiens)
1040	TPMTLVFGCRCSQLDHLIY	(L26914)	NOS III	(H sapiens)
380	GRMTLVFGCRHPPEEDHLIY	(U85094)	NOS	(O cuniculus)
1005	GDMILLFGCRHPDMDHIY	(U46504)	NOS	(G gallus)
481	GKNWLFFGNPHFTEDFLY	(M23008)	SR	(E coli)
915	GEVFLYLGSRHKREEYLY	(L26503)	SR	(S cerevisiae)
407	GRNWLIFGNRHFHRDFLY	(Z23169)	SR	(T roseopersicina)
261	GLAWLFLGVANVDSLLYD	(X99419)	FNR	(P sativum)
251	GLAWLFLGVPTSSSLLYK	(P00455)	FNR	(S oleracea)

Fig. 7C



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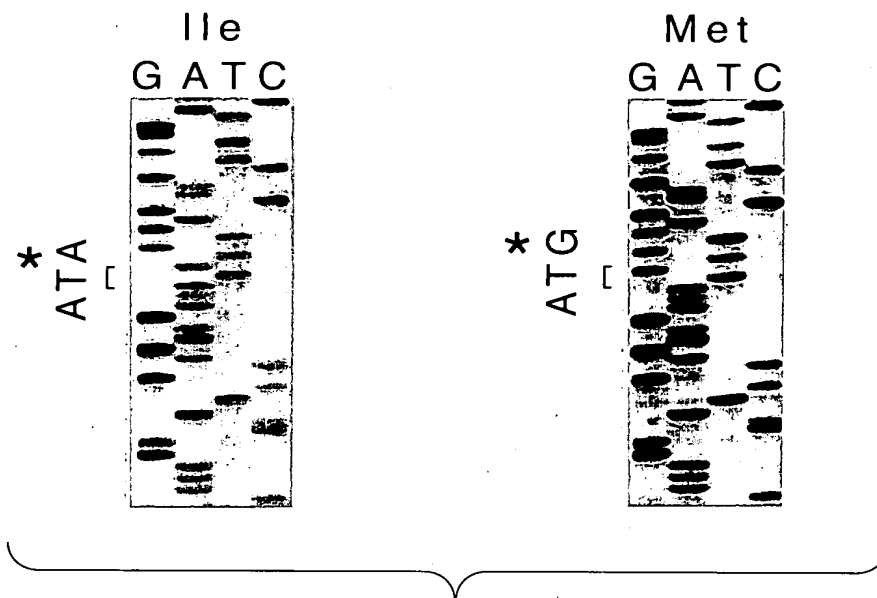


Fig. 8A

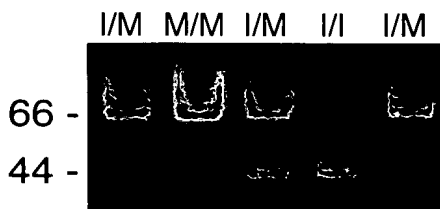


Fig. 8B